

RESEARCH MONOGRAPH . COMPOUND PROFILE

Modafinil

A benzhydryl sulfinyl acetamide approved for narcolepsy and shift work disorder, characterized by selective dopamine transporter binding and downstream histaminergic activation.

DOCUMENT	KDC-MN-016
ISSUED	2026-05-09
REVISION	1.0
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COMPOUND CLASS	Eugeroic / wakefulness-promoting agent

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ABSTRACT

Modafinil (CAS 68693-11-8; molecular formula C₁₅H₁₅NO₂S; molecular weight 273.35) is a wakefulness-promoting agent first synthesized at Laboratoire Lafon in France in the 1970s as the active metabolite of adrafinil and approved by the FDA in 1998 for excessive daytime sleepiness associated with narcolepsy, shift work sleep disorder, and obstructive sleep apnea. The compound is a racemic mixture; the (R)-enantiomer (armodafinil) carries the majority of the wakefulness-promoting activity and is marketed separately. The principal mechanism is binding to the dopamine transporter (DAT) with weak inhibitor affinity (K_i approximately 4 microM), producing modest extracellular dopamine elevation in the striatum and prefrontal cortex without the steep release kinetics characteristic of amphetamines or methylphenidate. Downstream effects include activation of orexinergic neurons in the lateral hypothalamus, elevation of histamine in the tuberomammillary nucleus, and increased glutamatergic tone in the prefrontal cortex with concurrent attenuation of GABAergic inhibition. The plasma half-life is 12 to 15 hours; oral bioavailability is high (greater than 80 percent); metabolism is hepatic via CYP3A4 and to a lesser extent via amide hydrolysis. Clinical efficacy in narcolepsy and shift work indications is well established; off-label use for cognitive enhancement in healthy individuals is widespread but the magnitude of cognitive benefit in healthy subjects is small and inconsistent across trials. Schedule IV in the United States. Common adverse events include headache, nausea, anxiety, and insomnia; rare serious events include Stevens-Johnson syndrome and DRESS. The compound is not a

controlled substance under international treaty but is regulated nationally in most jurisdictions.

1. Compound Identification

Modafinil is described as eugeroic / wakefulness-promoting agent. A benzhydryl sulfinyl acetamide approved for narcolepsy and shift work disorder, characterized by selective dopamine transporter binding and downstream histaminergic activation.

1.1 Class summary

Eugeroic / wakefulness-promoting agent

1.2 Subtitle

A benzhydryl sulfinyl acetamide approved for narcolepsy and shift work disorder, characterized by selective dopamine transporter binding and downstream histaminergic activation.

2. Abstract

Modafinil (CAS 68693-11-8; molecular formula C₁₅H₁₅NO₂S; molecular weight 273.35) is a wakefulness-promoting agent first synthesized at Laboratoire Lafon in France in the 1970s as the active metabolite of adrafinil and approved by the FDA in 1998 for excessive daytime sleepiness associated with narcolepsy, shift work sleep disorder, and obstructive sleep apnea. The compound is a racemic mixture; the (R)-enantiomer (armodafinil) carries the majority of the wakefulness-promoting activity and is marketed separately. The principal mechanism is binding to the dopamine transporter (DAT) with weak inhibitor affinity (K_i approximately 4 μM), producing modest extracellular dopamine elevation in the striatum and prefrontal cortex without the steep release kinetics characteristic of amphetamines or methylphenidate. Downstream effects include activation of orexinergic neurons in the lateral hypothalamus, elevation of histamine in the tuberomammillary nucleus, and increased glutamatergic tone in the prefrontal cortex with concurrent attenuation of GABAergic inhibition. The plasma half-life is 12 to 15 hours; oral bioavailability is high (greater than 80 percent); metabolism is hepatic via CYP3A4 and to a lesser extent via amide hydrolysis. Clinical efficacy in narcolepsy and shift work indications is well established; off-label use for cognitive enhancement in healthy individuals is widespread but the magnitude of cognitive benefit in healthy subjects is small and inconsistent across trials. Schedule IV in the United States. Common adverse events include headache, nausea, anxiety, and insomnia; rare serious events include Stevens-Johnson syndrome and DRESS. The compound is not a controlled substance under international treaty but is regulated nationally in most jurisdictions.

3. Mechanism of Action

Weak DAT inhibition (~4 microM Ki) with secondary orexinergic and histaminergic activation. Glutamate elevation and GABA attenuation in PFC. Distinct from amphetamine-class psychostimulants in lacking presynaptic monoamine release.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

100 to 200 mg per oral administration in clinical use; research literature reports doses up to 400 mg for sleep-deprivation studies.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. References

1. Mignot E, et al. Modafinil binds to the dopamine uptake carrier site. J Pharmacol Exp Ther 1994.
2. Wisor JP. Modafinil as a catecholaminergic agent. Front Neurol 2013.
3. Volkow ND, et al. Effects of modafinil on dopamine and dopamine transporters in the male human brain. JAMA 2009.
4. Battleday RM, Brem AK. Modafinil for cognitive neuroenhancement in healthy non-sleep-deprived subjects: a systematic review. Eur Neuropsychopharmacol 2015.
5. Robertson P Jr, Hellriegel ET. Clinical pharmacokinetic profile of modafinil. Clin Pharmacokinet 2003.

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